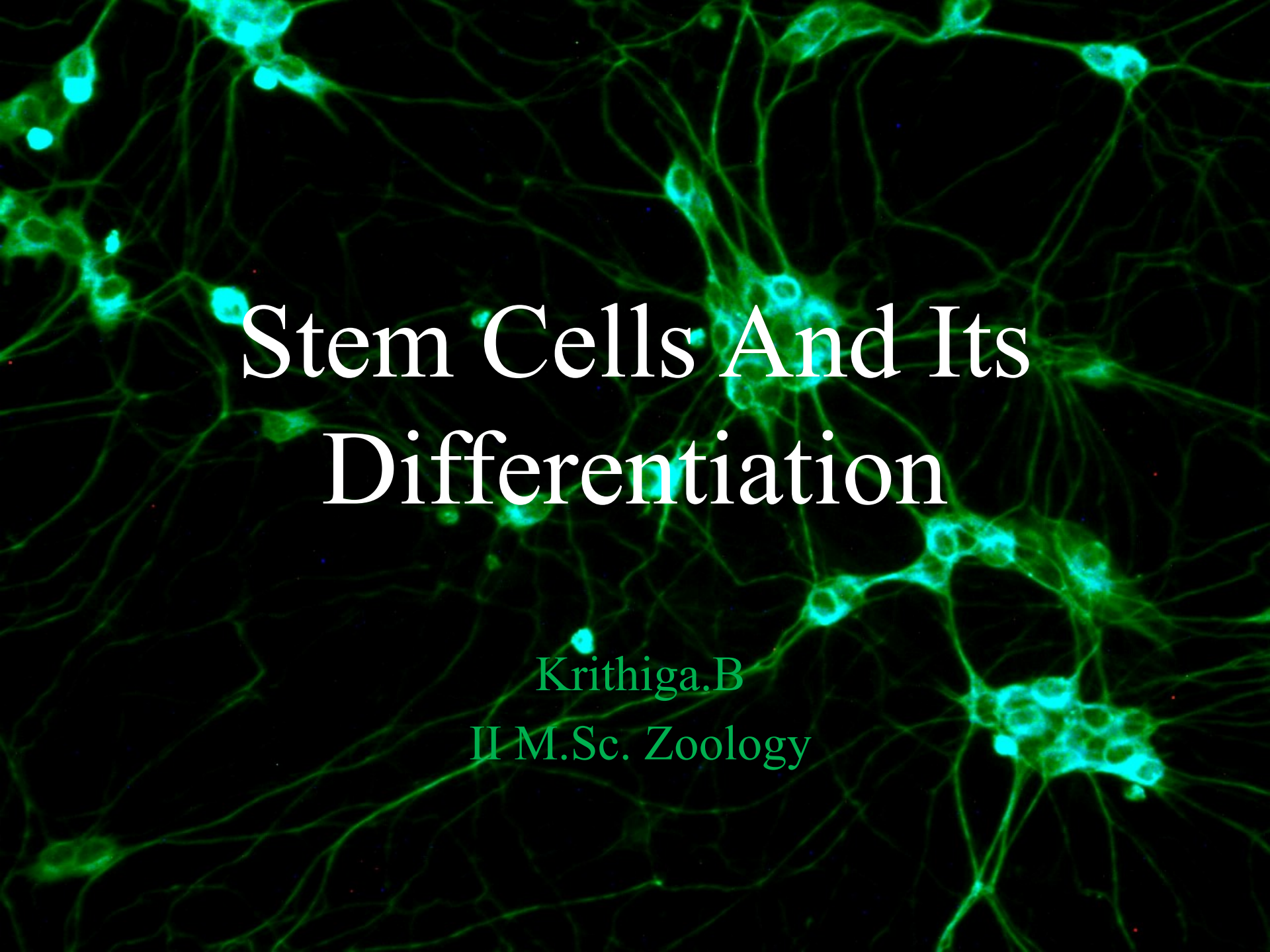
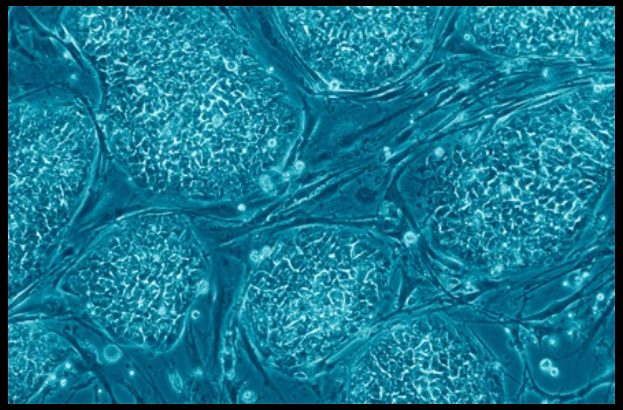


Stem Cells And Its Differentiation

Krithiga.B
II M.Sc. Zoology

What are stem cells..?

- A cell that has the ability to continuously divide and differentiate into various other kind(s) of cells/tissues.
- Classified into three broad categories, based on their ability to differentiate.
  - Totipotent, Pluripotent and Multipotent stem cells.



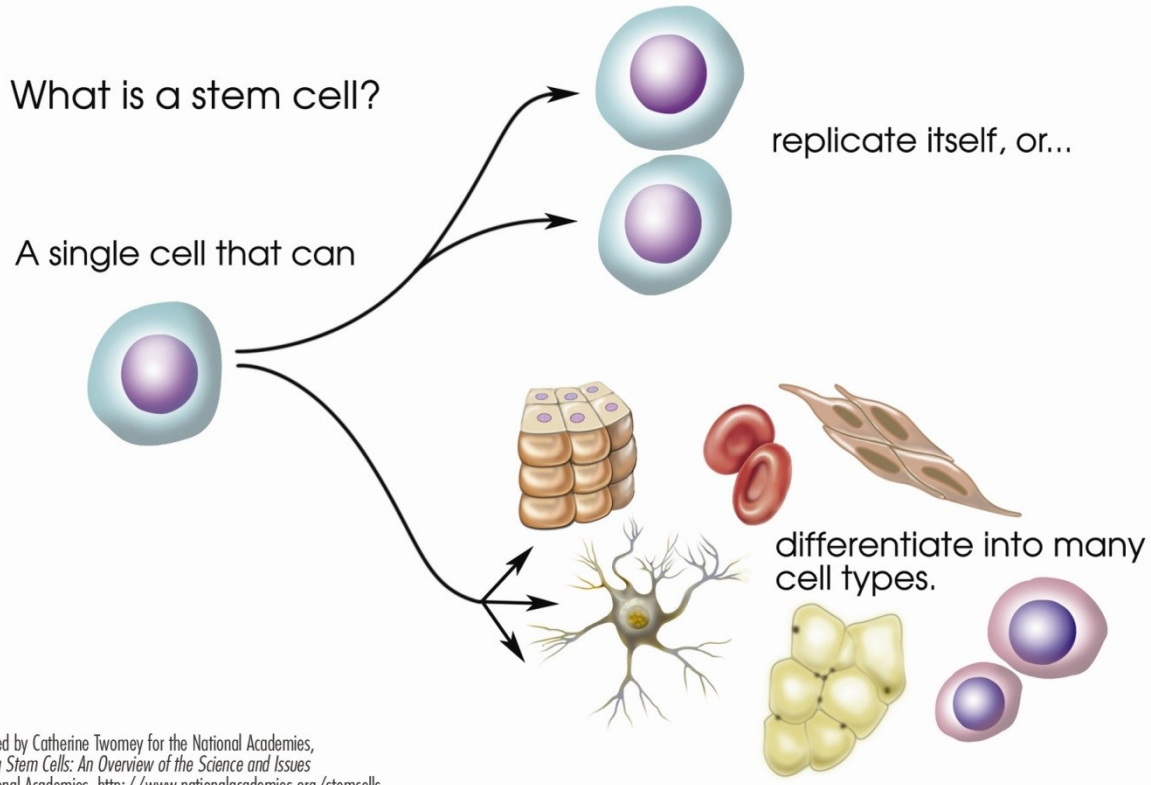


Image prepared by Catherine Twomey for the National Academies,
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, http://www.nationalacademies.org/stemcells.
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- Totipotent stem cells are found only in early embryos. Each cell can form a complete organism (e.g., identical twins).
- Pluripotent stem cells exist in the undifferentiated inner cell mass of the blastocyst and can form any of the over 200 different cell types found in the body.
- Multipotent stem cells are derived from fetal tissue, cord blood and adult stem cells.
  - ability to differentiate is more limited than pluripotent stem cells.
  - have a track record of success in cell-based therapies.

- Oligopotent stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.
- Unipotent cells can produce only one cell type, their own, but have the property of self-renewal which distinguishes them from non-stem cells (e.g. muscle stem cells).

Unique Properties Of All Stem Cells

- Capable of dividing and renewing themselves for long periods.
- Are unspecialized/ undifferentiated.
- Can give rise to specialized cell types.

Why are they important?

- Because stem cells can turn into any other cell, they serve as a major repair mechanism of the body.
- Research has shown that stem cells can recognize areas of need, and migrate into those areas, then multiply and differentiate into the exact cells needed to repair the tissues and organs that have been damaged.

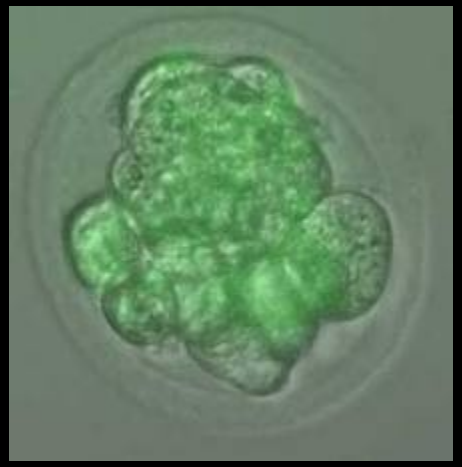
Sources Of Stem Cells

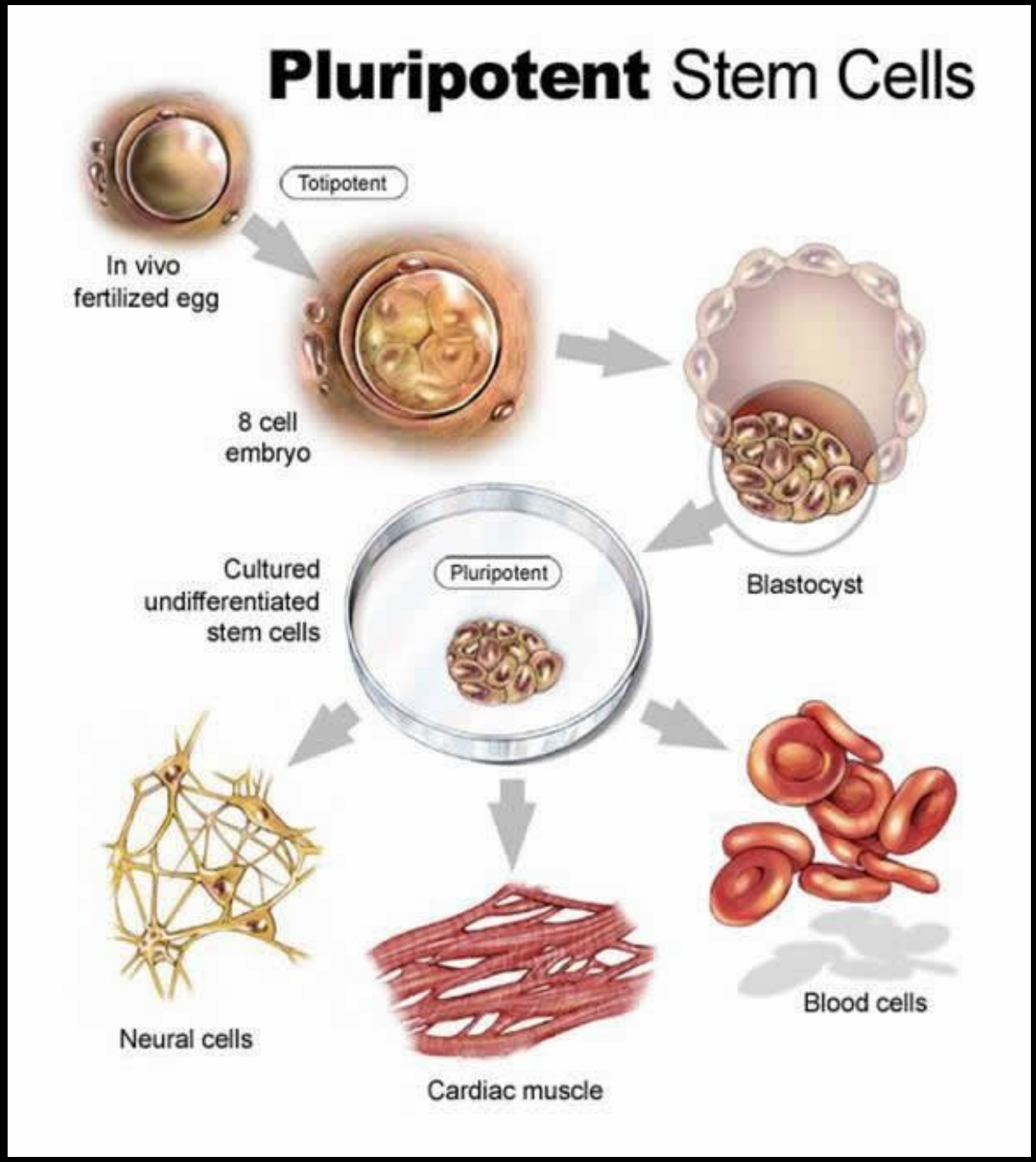
- **Embryonic stem cells**
- **Fetal stem cells**
  - germ line tissues that make up the gonads of aborted fetuses.
- **Umbilical cord stem cells**
- **Placenta derived stem cells**
- **Adult stem cells**
  - Bone marrow, blood stream, human eye, dental pulp, liver, skin, gastrointestinal tract and pancreas.

Embryonic Stem Cells

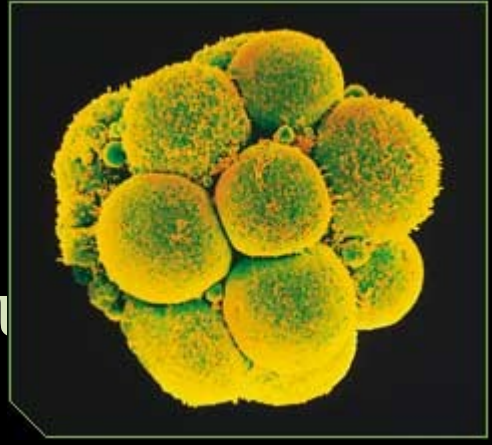
- Pluripotent.
- Derived from embryos (blastocyst, 12 days stage) that develop from eggs that have been fertilized in vitro in an in vitro fertilization clinic and then donated for research purposes with informed consent of the donors.
- Not derived from eggs fertilized in a woman's body.
  - Ethical issues.

- Do not have the ability to grow by themselves
  - grown on mouse cell feeder layers.
- These cells are prone to form tumors (cancer) when transplanted
  - hence their clinical (therapeutic) use is questionable.

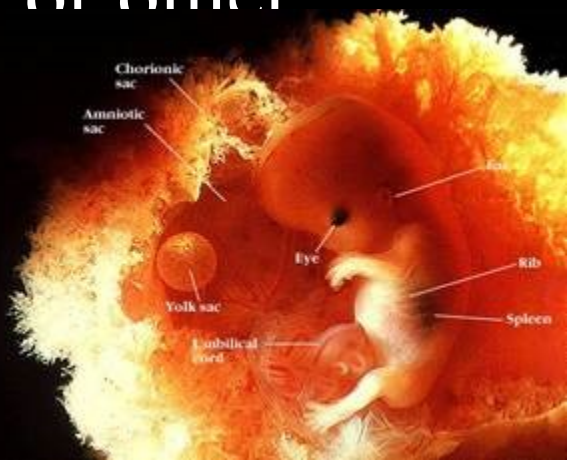



Pluripotent Stem Cells
Totipotent
In vivo
fertilized egg
8 cell
embryo
Blastocyst
Cultured
undifferentiated
stem cells
Pluripotent
Neural cells
Cardiac muscle
Blood cells

Fetal Stem Cells



- Harvested from **aborted human fetu**
- Poses obvious ethical questions.
- These cells are harvested from fetuses whose mothers have already decided to abort.
- Since these cells are the result of an abortion, there is a risk that the fetal materials have been contaminated with mothers' blood or other materials.



- Adult blood cells can react against the transplant recipient's tissue, or cause an immune reaction by the recipient against the contaminated fetal cells.
- Contaminated stem cells may be sensitized against adult blood, thus causing a "graft vs host disease" problem after transplantation.
- Another concern with these fetal cells is the apparent lack of screening for infectious diseases in these tissues.

Umbilical cord stem cells

- Pluripotent.
- Unlike embryonic stem cells, Umbilical Cord Stem Cells do not promote tumors.
- Unlike fetal stem cells, Umbilical Cord Stem Cells do not require the death of a human baby or fetus.

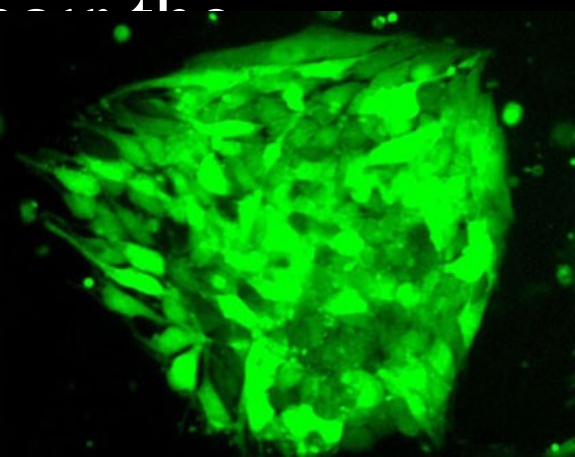
- Unlike adult stem cells, Umbilical Cord Stem Cells do not cause immune reaction. Since these immature cells do not express adult tissue-type proteins (ABO, Rh, and HLA antigens) on their surfaces, these proteins do not seem to cause either an immune reaction in the recipient, or a graft vs host reaction against the recipient.

Placenta Derived Stem Cells

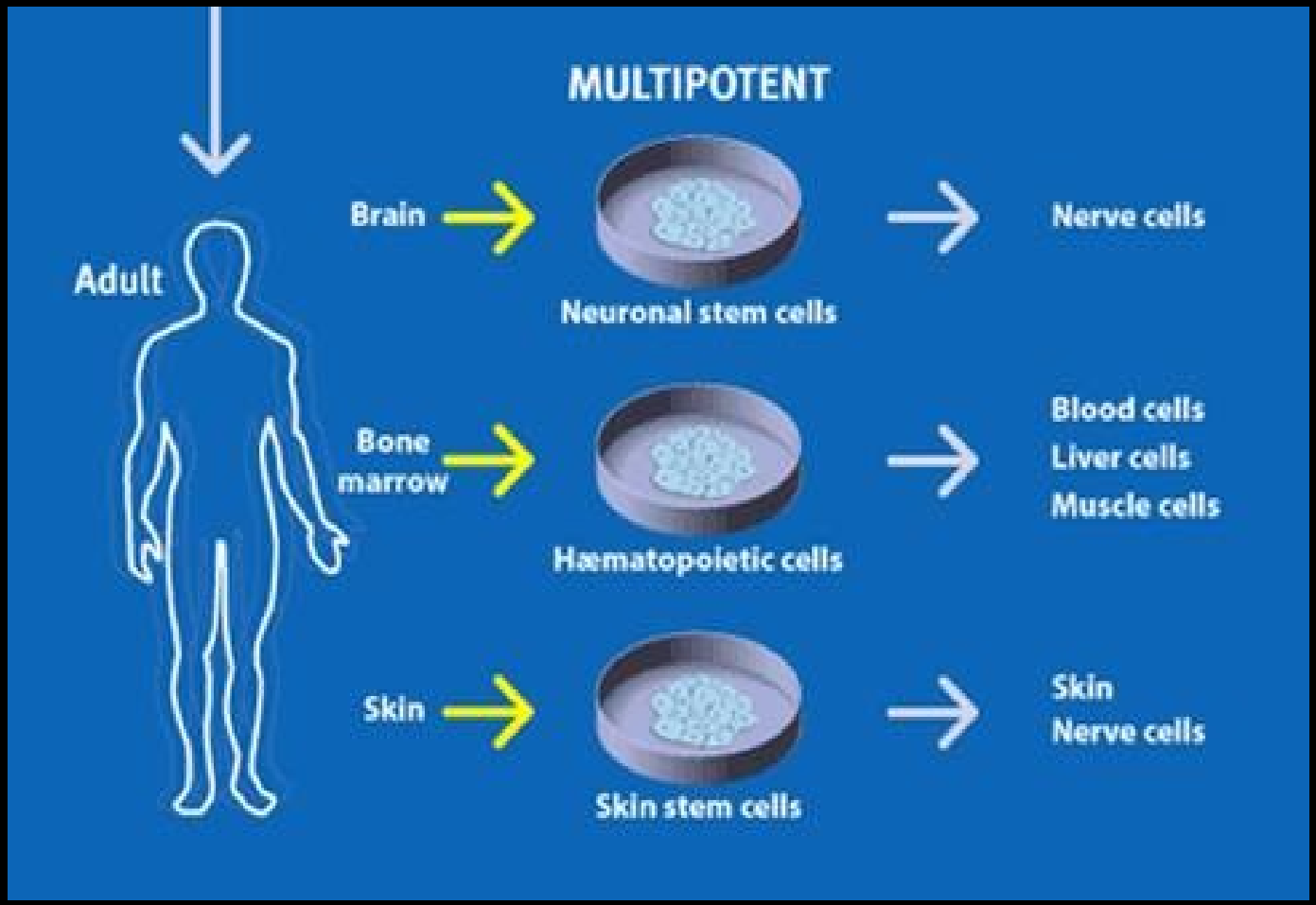
- Up to ten times as many stem cells can be harvested from a placenta as from cord blood.
- .At birth, the umbilical cord is cut, and the cord and placenta are usually discarded as medical waste.
- The blood is collected from the placenta and cord within 5 minutes of birth, and placed in a special bag with a solution that prevents clotting.
- The blood is transported to the lab within 24 hours. Stem cells are separated from the blood using a centrifuge or other methods.

Adult Stem Cells

- Adult or somatic stem cells exist throughout the body after embryonic development and are found inside of different types of tissue.
- They remain in a quiescent or non-dividing state for years until activated by disease or tissue injury.
- Primary role is to maintain and rep[illegible] tissue in which they are found.



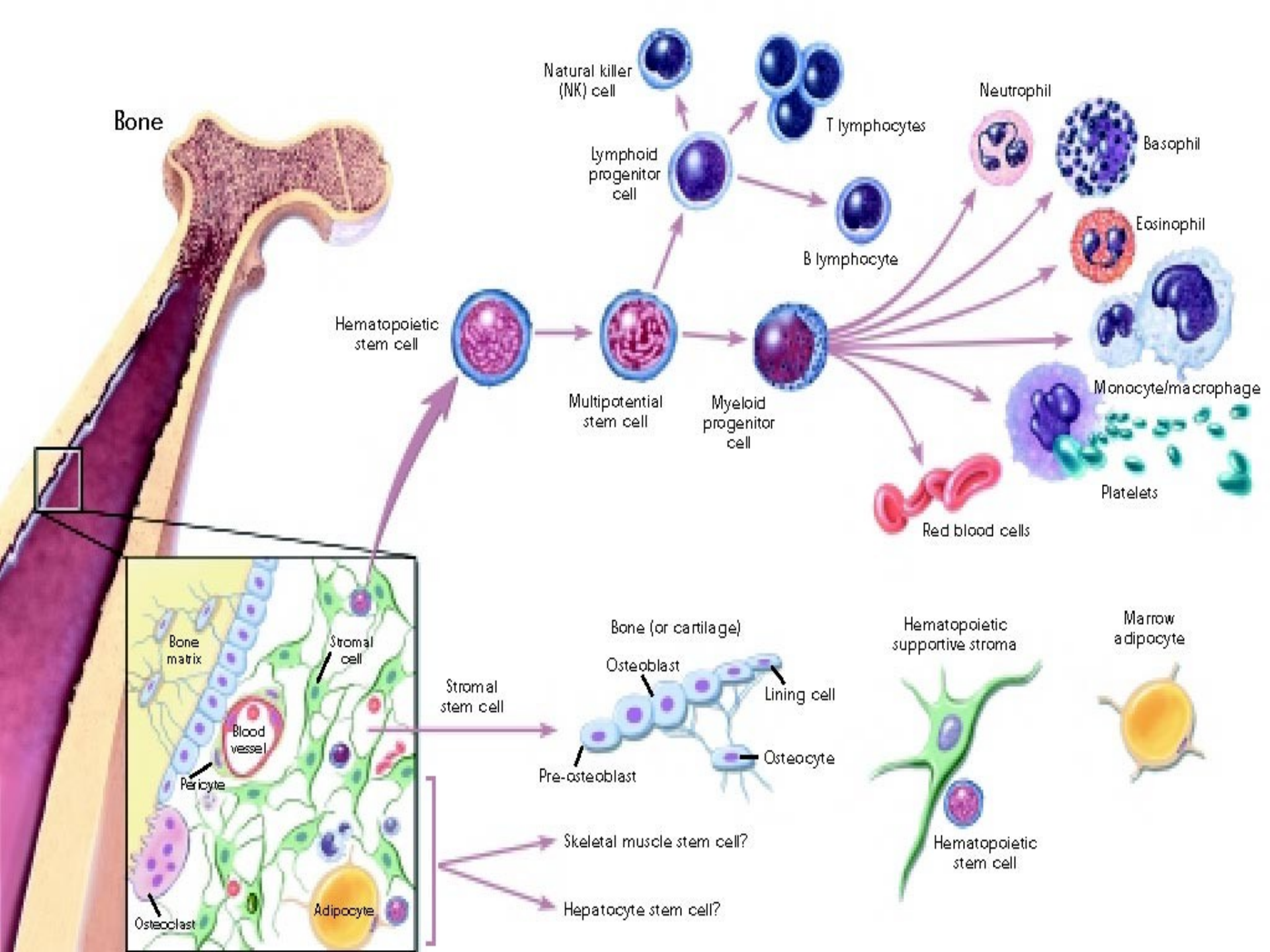
- They are called multipotent, because they have the ability to turn into a few types of cells.
- Adult stem cells can divide or self-renew indefinitely, enabling them to generate a range of cell types from the originating organ or even regenerate the entire original organ.
- Sources include biopsies of adult fat, muscle, bone marrow, blood, or liposuction fluid.

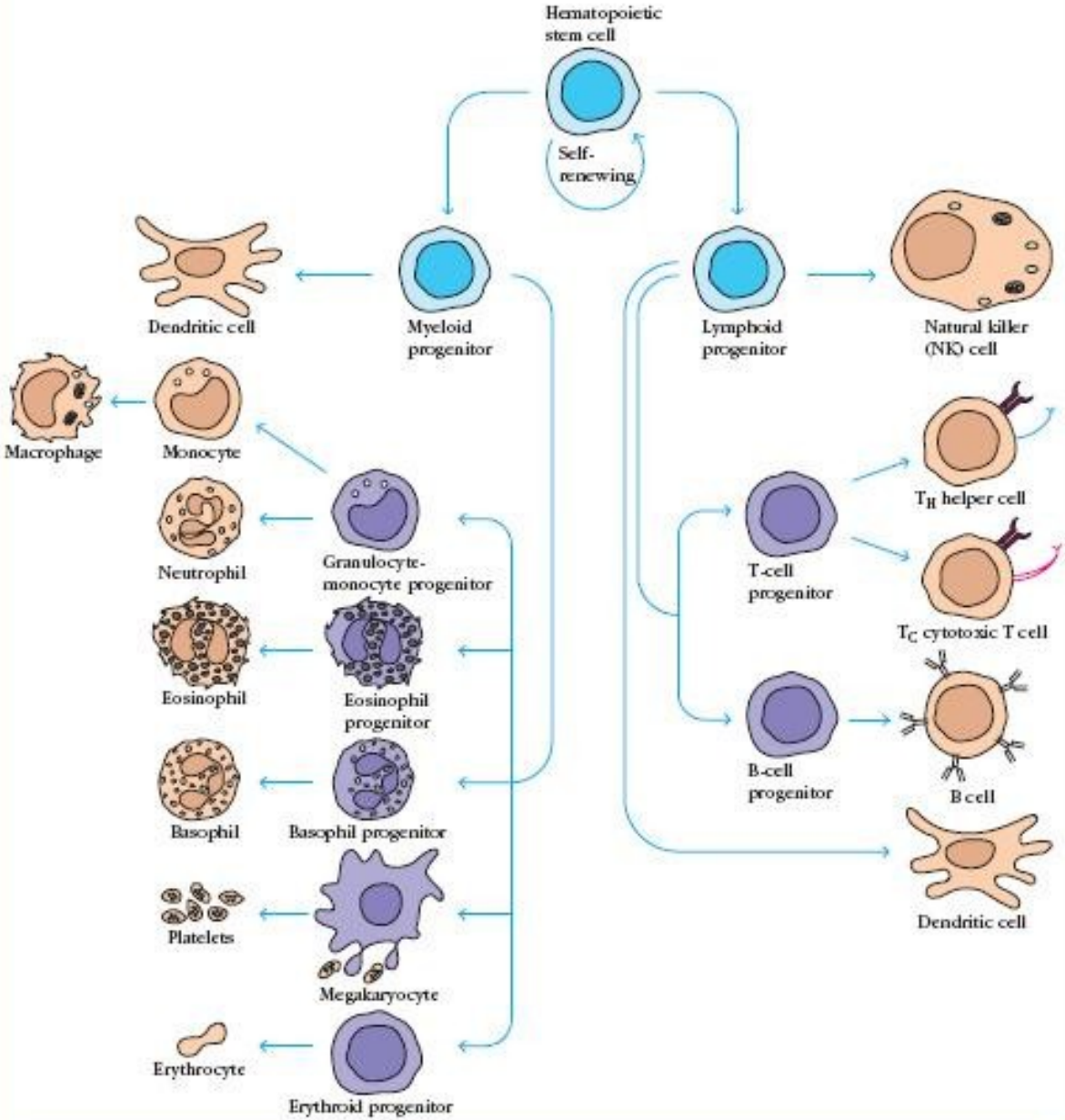

MULTIPOTENT
Adult
Brain
Neuronal stem cells
Nerve cells
Bone marrow
Hæmatopoietic cells
Blood cells
Liver cells
Muscle cells
Skin
Skin stem cells
Skin
Nerve cells

- Cells do not require other cells for their growth.
- They do not promote tumors.
- But because they are from tissues that fully express the tissue type, they can cause immune reactions when implanted into a person different from the donor.

Differentiation Of Bone Marrow Stem Cells

- In the 1950s, researchers discovered that the bone marrow contains at least two kinds of stem cells.
  - hematopoietic stem cells - forms all the types of blood cells in the body.
  - bone marrow stromal stem cells (also called mesenchymal stem cells, or skeletal stem cells).
    - These non-hematopoietic stem cells make up a small proportion of the stromal cell population in the bone marrow, and can generate bone, cartilage, fat, cells that support the formation of blood, and fibrous connective tissue.


Bone
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Monocyte/macrophage
Platelets
Red blood cells
Bone matrix
Stromal cell
Blood vessel
Pericyte
Osteoclast
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte



Hematopoiesis. Self-renewing hematopoietic stem cells give rise to lymphoid and myeloid progenitors. All lymphoid cells descend from lymphoid progenitor cells and all cells of the myeloid lineage arise from myeloid progenitors. Note that some dendritic cells come from lymphoid progenitors, others from myeloid precursors.

- Stromal cells or non hematopoietic cells
  - Support the growth and differentiation of HSC.
  - Influences the differentiation by providing Hematopoietic Inducing Microenvironment (HIM).
  - HIM contains cellular matrix & growth promoting factors-
    - Soluble agents that arrive at target cell by diffusion,
    - Membrane bound stromal cells- that require cell to cell contact.

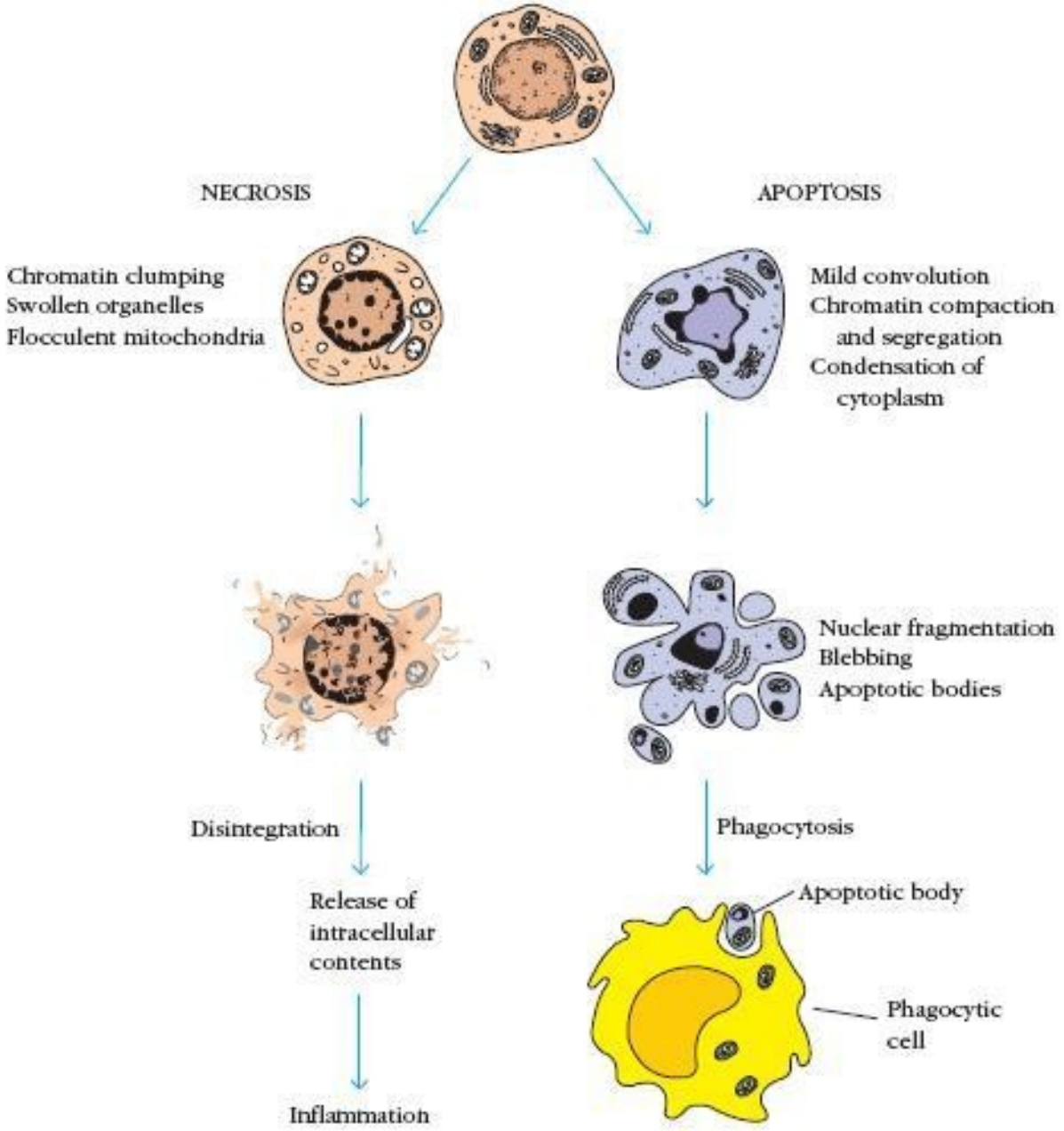
- During infection, hematopoiesis is stimulated by the production of hematopoietic growth factors by activated macrophages and T cells.
  - Cytokines
  - Colony stimulating factors
    - Induces the formation of distinct hematopoietic cell lines.
  - Erythropoietic glycoprotein
    - Regulates production of RBC

Hematopoietic Homeostasis

- Erythrocytes - life span - 120 days.
- WBC – life span ranges from few days for neutrophils to 20-30 years for some T lymphocytes.
- To maintain a steady state - the body should produce $3.7 * 10^{11}$ WBC/day.
- Programmed cell death / apoptosis is an essential homeostatic mechanism

Apoptosis

- Morphological changes:
  - Pronounced increase in cell volume.
  - Modification of the cytoskeleton – results in blebbing.
  - Condensation of the chromatin.
  - Degradation of the DNA into small fragments.
- Macrophages phagocytose apoptotic bodies.



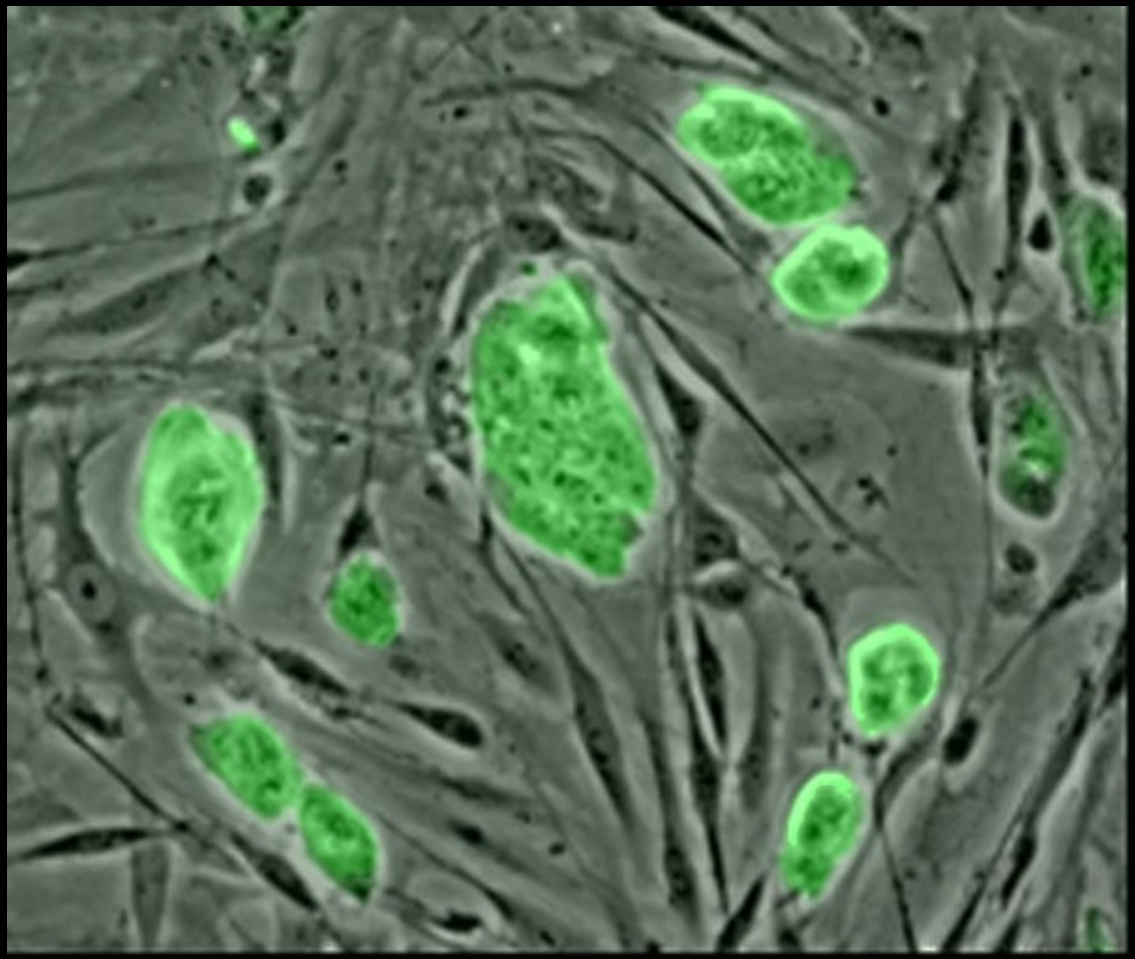
Comparison of morphologic changes that occur in apoptosis and necrosis. Apoptosis, which results in the programmed cell death of hematopoietic cells, does not induce a local inflammatory response. In contrast, necrosis, the process that leads to death of injured cells, results in release of the cells' contents, which may induce a local inflammatory response.

Transdifferentiation

- A number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted lineage (i.e., brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells, and so forth).
- This reported phenomenon is called transdifferentiation.

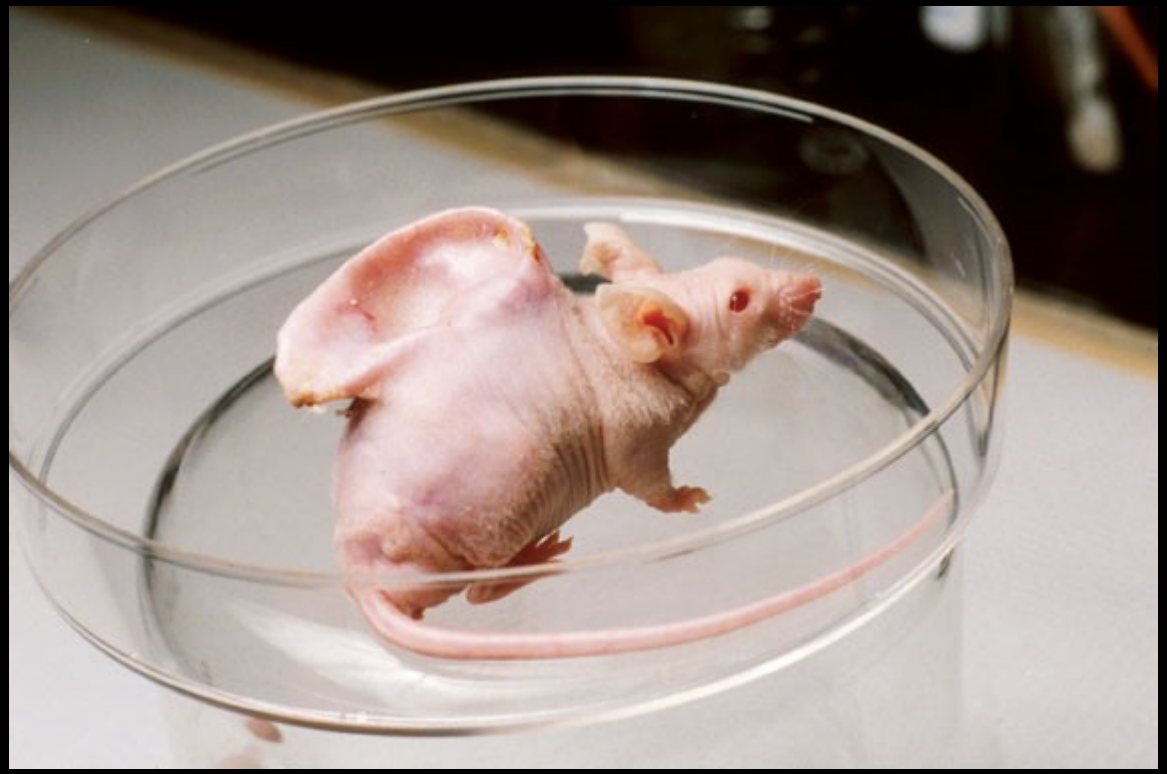
Induced Pluripotent Stem Cells

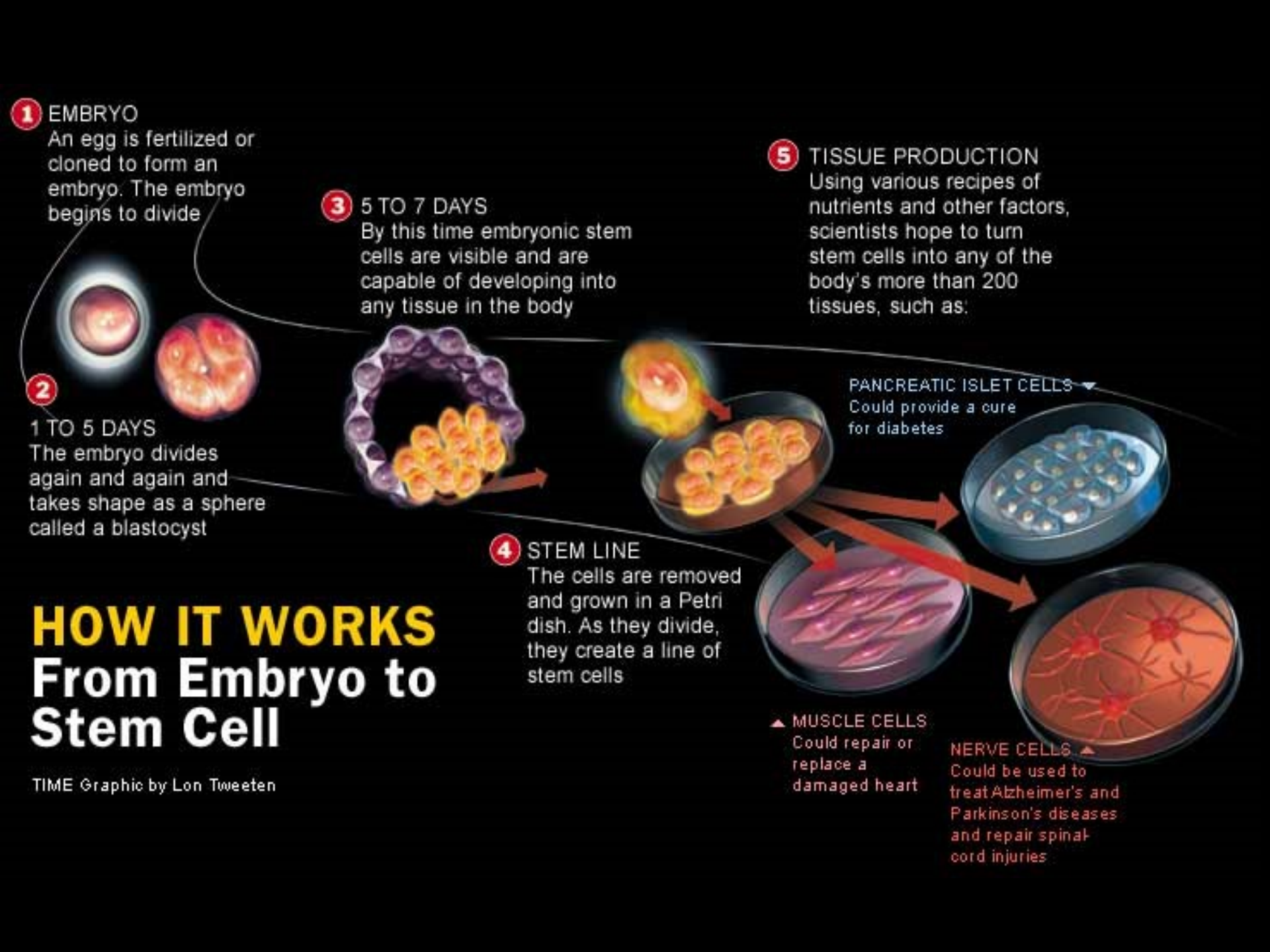
- **Induced pluripotent stem cells (iPSCs)** are adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.
- Induced Pluripotent Stem Cells are similar to natural pluripotent stem cells, such as embryonic stem (ES) cells, in many aspects but the full extent of their relation to natural pluripotent stem cells is still being assessed.

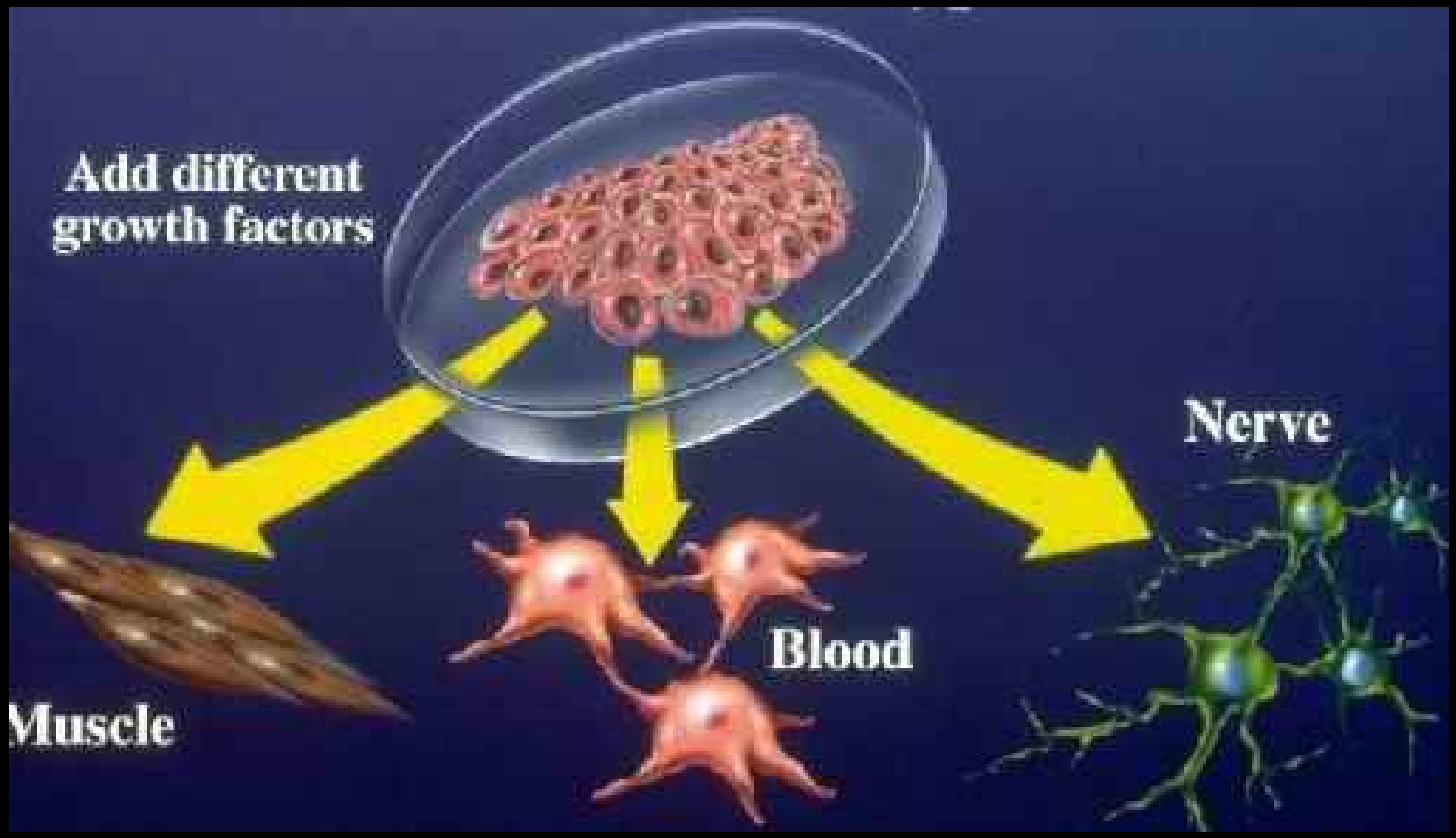


Chimeras

- A chimera is an organism that has both human and animal cells or tissues.
- Often in stem cell research, human cells are inserted into animals (like mice or rats) and allowed to develop.
- This creates the opportunity for researchers to see what happens when stem cells are implanted.
- Many people, however, object to the creation of an organism that is "part human".

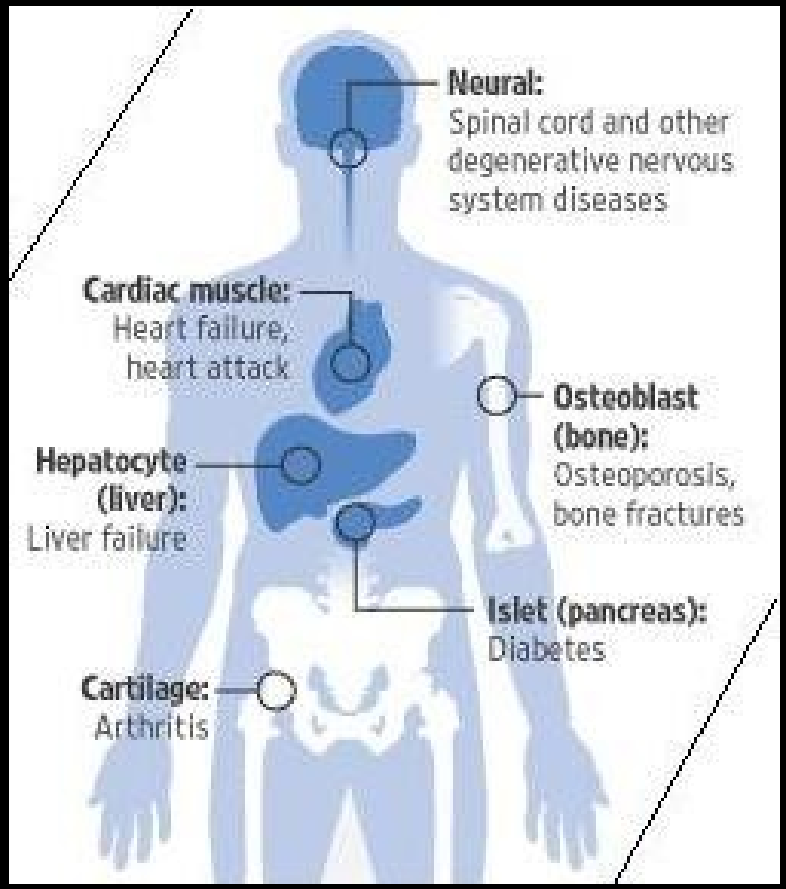



1 EMBRYO
An egg is fertilized or cloned to form an embryo. The embryo begins to divide
2 1 TO 5 DAYS
The embryo divides again and again and takes shape as a sphere called a blastocyst
3 5 TO 7 DAYS
By this time embryonic stem cells are visible and are capable of developing into any tissue in the body
4 STEM LINE
The cells are removed and grown in a Petri dish. As they divide, they create a line of stem cells
5 TISSUE PRODUCTION
Using various recipes of nutrients and other factors, scientists hope to turn stem cells into any of the body's more than 200 tissues, such as:
PANCREATIC ISLET CELLS
Could provide a cure for diabetes
MUSCLE CELLS
Could repair or replace a damaged heart
NERVE CELLS
Could be used to treat Alzheimer's and Parkinson's diseases and repair spinal-cord injuries
HOW IT WORKS
From Embryo to Stem Cell
TIME Graphic by Lon Tweeten

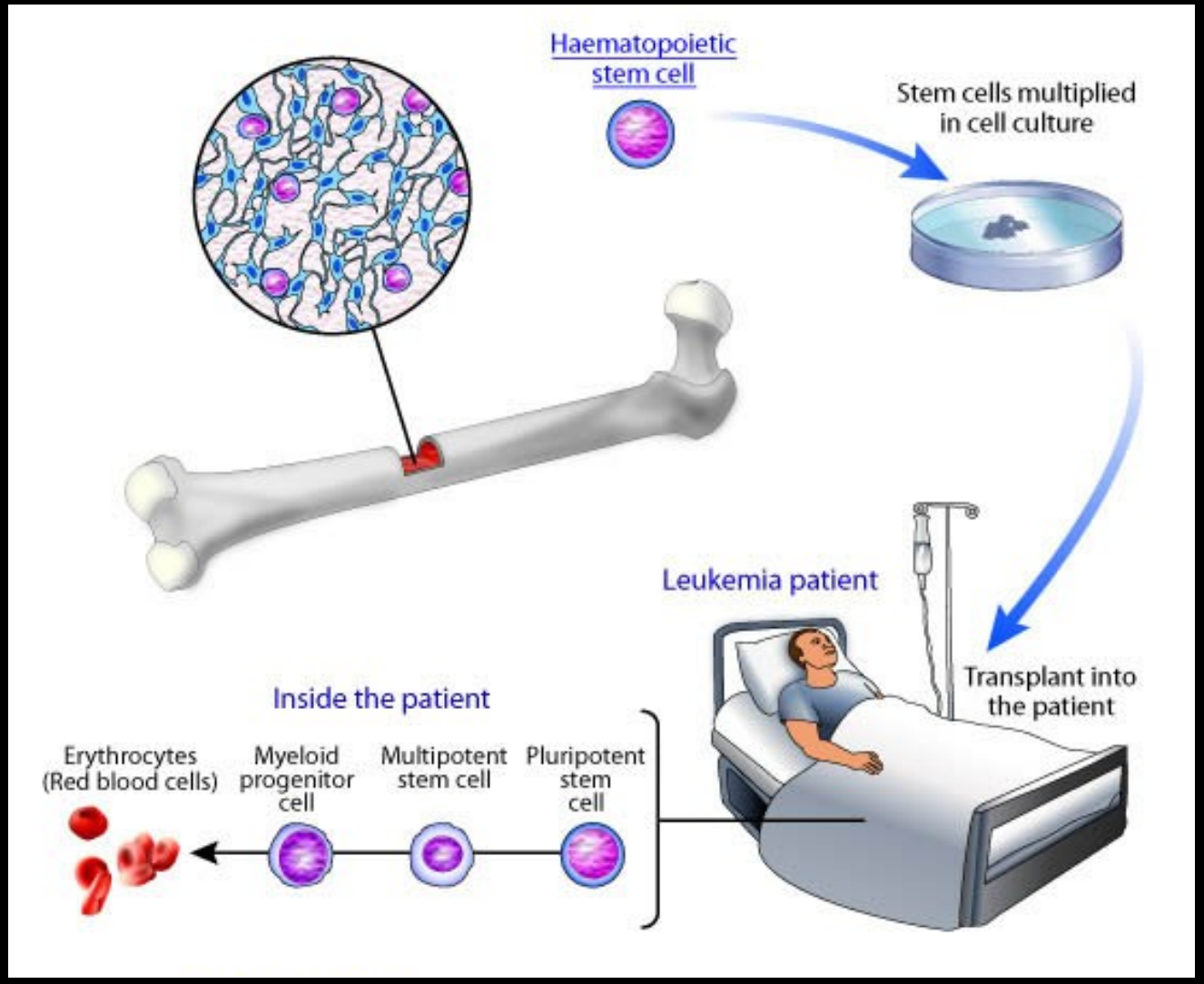

Add different
growth factors
Nerve
Blood
Muscle

Applications

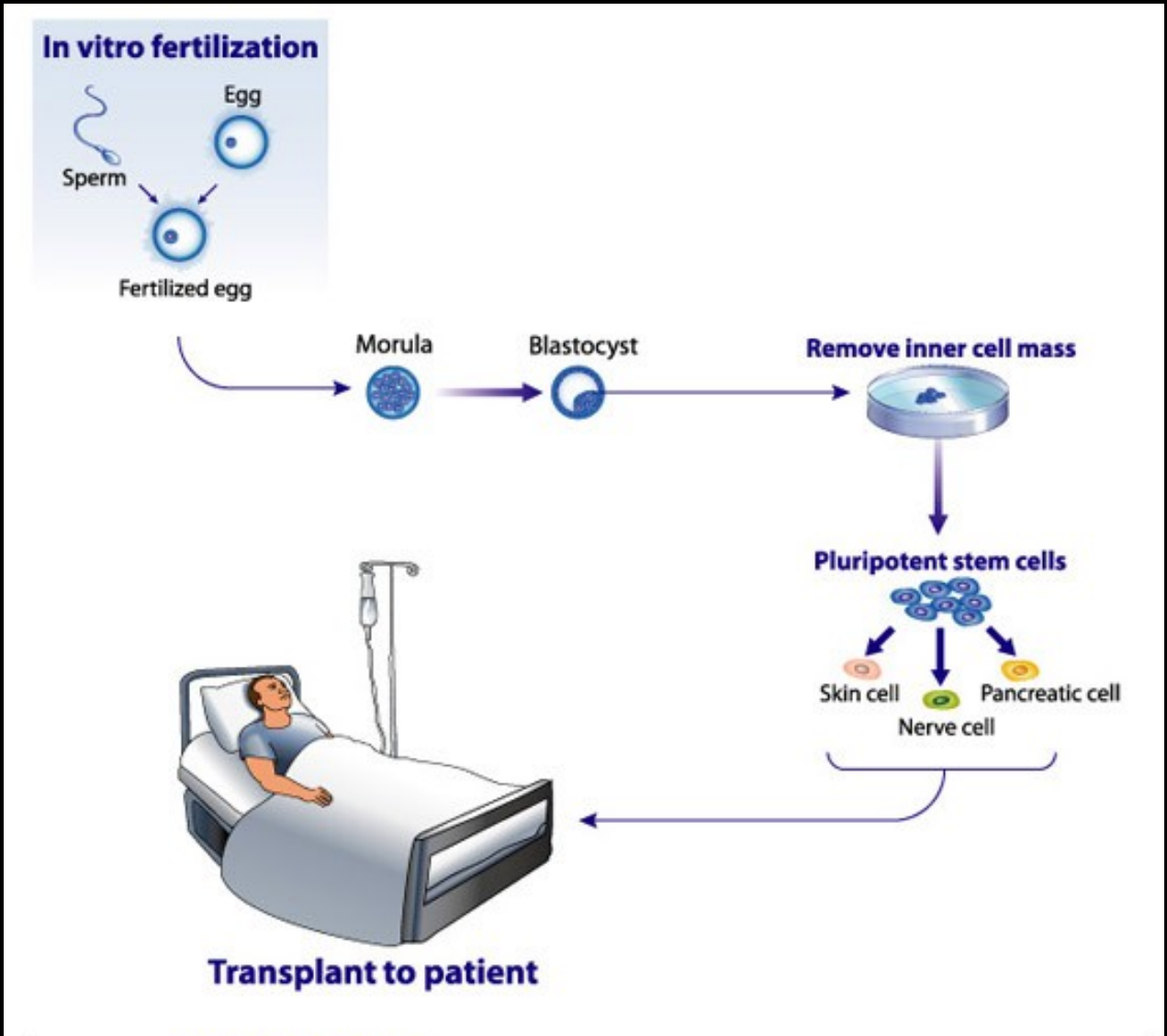
- Organ transplants
- Parkinson's disease
- Alzheimer's
- Diabetes
- Heart disease
- Spinal cord injury
- Burns
- Vision loss



Leukemia Treatment

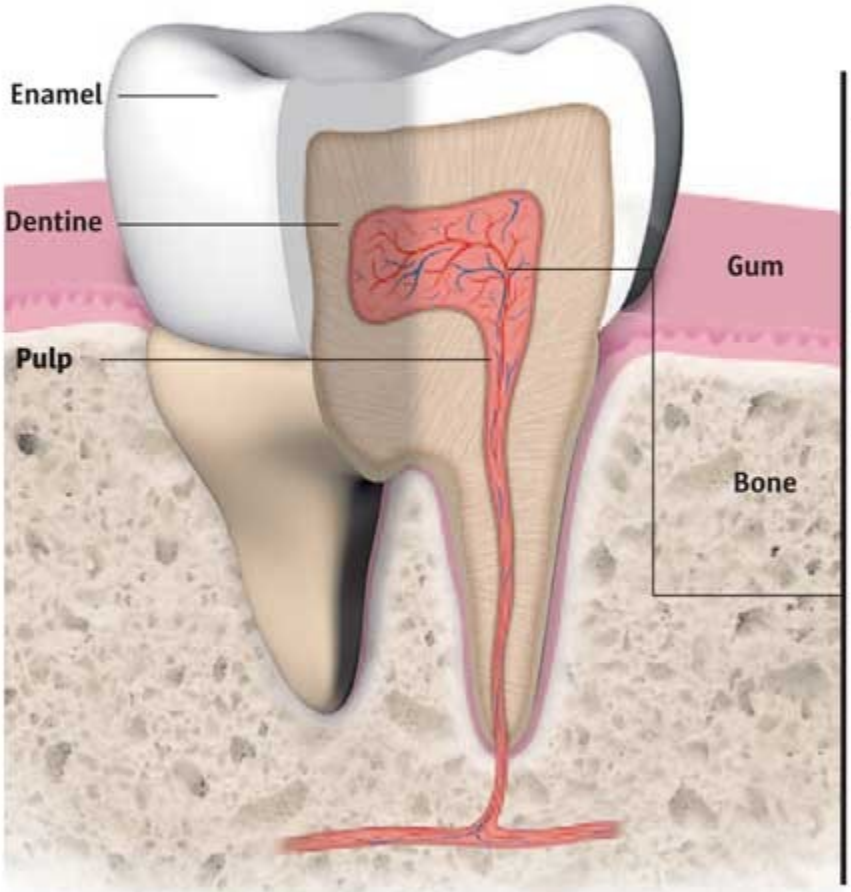


Treatment through Transplant



Pulling stem cells from teeth

Research involving stem cells in teeth has exploded during the past four or five years and companies that will bank the cells in a deep-freeze have since begun operating. Company officials and their scientists say dental stem cells have the potential to treat a variety of diseases, including heart disease, leukemia and Parkinson's. In the nearer future, dental stem cells could grow new teeth and jaw bone. Other scientists caution people against spending money to bank their stem cells.



Stem cells are in areas next to nerve and blood vessels within the pulp of the tooth. Companies that bank stem cells say cells that can be regenerated from dental stem cells will someday include:

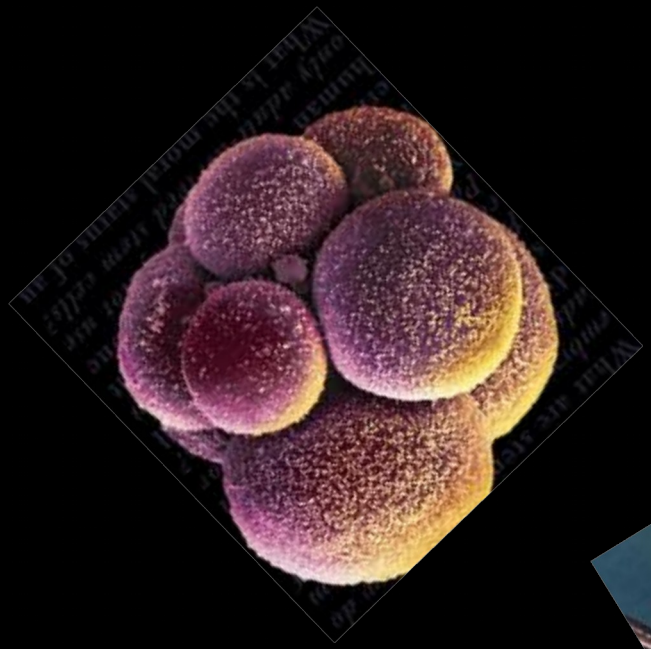
- Nerve and spinal cord
- Brain
- Heart
- Liver
- Bone
- Ligaments and cartilage
- Muscle
- Skin

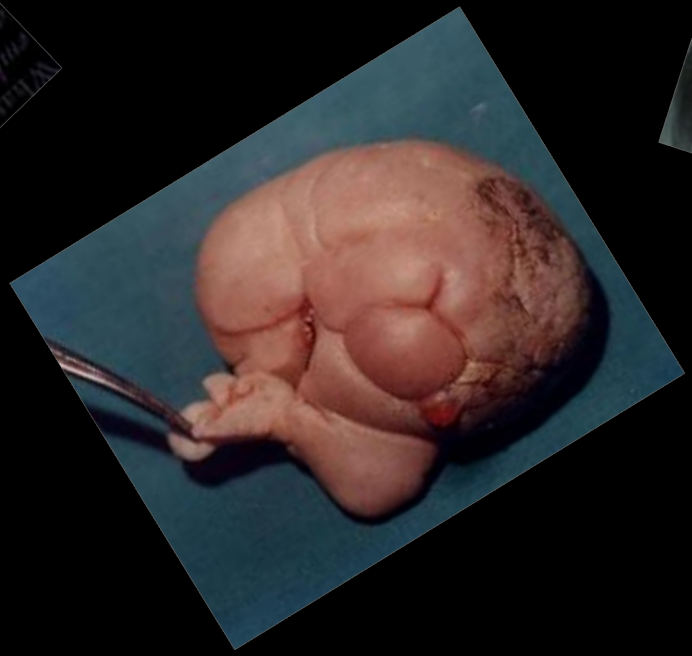
Source: StemSave; National Institutes of Health; The Human Body

Thomas McKay, The Denver Post

Sight restored in less than a month using stem cell contact lenses

Stem cell controversy…





Thank You